A Case Report of Neuroleptic Malignant Syndrome Induced by Clozapine

Is Neuroleptic Malignant Syndrome Diagnostic Criteria Adequately Sensitive to Identify Diverse Features of the Syndrome?

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Introduction

Neuroleptic Malignant Syndrome (NMS) is a rare fatal medical complication that occurs as a result of dopaminergic receptor blockage in the caudate at the termination of the nigrostriatal pathways (1), and may occur at any time following consumption of dopamine antagonists. This disorder also occurs in cases of sudden discontinuation of dopamine agonists and antagonists (2,3). Some studies have also reported the syndrome following tricyclic antidepressants (TCAs) or specific serotonin reuptake inhibitors (SSRIs) use (4).

The syndromes manifestations are high fever, extra-pyramidal symptoms, and dysfunctions in autonomic system, such as unstable blood pressure, cardiac arrhythmia, dyspnea,sweating, and urinary incontinence(5).

The incidence has been reported from 0.69 to 3.23percent (6,7).

A review of 16 studies by Carrof, has reported incidence rates of 0.196% (8). In another study on 7, 8708 individuals who were taking dopamine antagonists, NMS occurred in 19 cases; in which the incidence rate was 0.024% (9).

According to several studies, the NMS incidence rates have decreased during the recent years (6, 10-13); a 7 time decrease was reported in one study (10).

However, few researchers including Adityanjee et al. believe in factors such as limitations in study designs as the main reason for the decrease in incidence reports (11). Also, early diagnosis and treatment must be considered as another reason for the incidence decline (11). The incidence risk following atypical anti-psychotic drugs is much lower compare to typical ones. The increasing use of antipsychotic drugs reduces the MNS incidence as well (14).

Early diagnosis and treatment of the disorder is important. There are several reports of NMS following the use of atypical anti-psychotics including risperidone (15), clozapine(15), olanzapine(15,16) and quetiapine (17). Specially atypical presentations have been reported with clozapine (18) and olanzapine (19). Furthermore, the emergence of NMS with other medications such as TCAs and SSRIs along with high mortality rate of the syndrome (4), have brought the early interventions into special importance.

The following case is reported because there are only few reports of NMS with clozapine, and also due to atypical presentations of the case.

Case Report

The patient was a 52-year old married man

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who had been receiving treatment for paranoid schizophrenia (according to DSM-IV-TR) with several admissions for the past five years.

He was admitted due to a relapse to a psychiatric hospital in Tehran in May 2007. There were no history of any noticeable physical problems and the results of all laboratory tests were normal. He was on clozapine for 3.5 months, when the problem presented. He was taking clozapine, 400 mg daily and clonidine 0.2 mg daily in August 2007, at the time of NMS emergence. First, he had a fever of 38.2 degrees centigrade, sweating, drooling and mild rigidity in extremities, followed by a decrease in the level of consciousness (GCS= 6-7) and only responsive to painful stimuli. The blood pressure was 100/60 mmHg, pulse rate 110-120/ min. The CTscan was normal and the results of laboratory investigations were as follows:

Serum sodium (Na), potassium (K), aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubine and fasting blood sugar (FBS) level were in normal range; Patient's serum creatine phosphokinase (CPK) level was 1240 IU/L, serum lactic dehydrogenase (LDH) 645 IU/L, and white blood cell (WBC) count of 9000/mm3. The differential diagnoses of NMS such as heat stroke, metabolic tetanus, septicemia, CNS infection were ruled out clinically. Clozapine was discontinued while hydration and dantrolene 80mg qid started. The body temperature became normal after 3 days and the level of consciousness increased.

LDH equaled 318 IU/L and CPK 800 IU/L on the third day, and by the fourth day all the symptoms disappeared.

Discussion

In summary, the patient had a severe decline in the level of consciousness, mild muscular rigidity, fever, drooling, sweating, elevated blood pressure, but no instability in autonomic function. NMS was diagnosed according to DSM-IV-TR in which the disorder is defined by the presence of severe muscle rigidity, elevated temperature, and other related findings (e.g., diaphoresis, dysphagia, incontinence, changes in level of consciousness ranging from confusion to coma, mutism, elevated or labile blood pressure, elevated creatine phosphokinase (20). Although the NMS criteria are specific, the presentation of this disorder is so variable, that needs further precise clinical investigations (21).

However, fever and muscular rigidity are the most accepted symptoms in various studies. Our case presented both of theses symptoms, along with meeting other criteria (20).

Some clinicians have suggested NMS variants. In specific conditions called "atypical" *formes frustes* and incipient NMS, the patient may present most, but not all of the symptoms. The idea of the disorder variants was introduced from the beginning of NMS definition (21). The rigidity only in extremities instead of general muscular rigidity, observed in our case was also a variant symptom.

The important unanswered question is whether NMS is a spectrum of a different presentation.

Our case showed inconsistent symptoms and signs such as mildness of extra pyramidal symptoms and muscular rigidity. In other studies with clozapine, the clinical presentations including extra pyramidal symptoms were found to be less prominent as well (18,22). In one study, muscular rigidity was present in 36% of cases receiving clozapine (23), while it was reported to be 97-98% in previous studies (8, 24, 25).

A study by. Hasan and Buckley showed that clinical presentations are the same following administration of typical and atypical anti-psychotic medications, but CPK rises more with the typical anti-psychotics (22); a finding which was inconsistent with other investigations (26).

Carrof et al. in 2000 found that fever and other presentations are milder in NMS, following atypical anti-psychotics (27). Similarly, our case showed a low level of fever and mild extra pyramidal symptoms. Moreover, at anytime following the consumption of clozapine the disorder may occur. There are reports of the disorder 10 and 30 years after the onset of treatment (18, 28).

As previously stated, although NMS occurs less frequently with the atypical anti-psychotics, it appears its incidence is increasing with more prescriptions of these drugs (14). Perhaps the increase is due to the rise in atypical forms of the disease (29) caused by different therapeutic mechanisms of the modern medications (30).

A review by Hasan and Buckley, of 19 studies regarding NMS with clozapine and 13 with risperidone, discovered that 9 cases (47%) with clozapine and 8 cases (62%) with risperidone met the NMS criteria (22). This indicates that NMS induced by atypical anti-psychotics has atypical or partial presentations (11, 22, 27, 29-31). This has been confirmed by several studies. The atypical types are as hazardous as the typical ones, thus, in need of careful clinical diagnosis (29).

However, it should be noted that NMS of typical anti-psychotics might also be variable or heterogeneous (27). A few authors believe that the partial forms are prevalent, making psychiatrists aware of early intervention for the problem (22, 27, 31).

It seems that there have been many atypical cases similar to our case that might have been missed due to mild presentations and incomplete meeting of DSM-IV criteria for the disorder (29). The theory implies that the atypical forms would develop to typical NMS if not intervened properly.

In conclusion, NMS includes a spectrum of symptoms and signs which implies the need for a revision to the diagnostic criteria. The disorder overlaps with multiple CNS problems such as serotonin syndrome, malignant hyperthermia and lethal catatonia. The severe Serotonin syndrome following administration of monoamine oxidase inhibitors (MAOIs) and other medications, presents with delirium, high blood pressure, muscular rigidity and high body temperature.

Malignant hyperthermia, which is a drug reaction presents with autonomic instability, muscular rigidity and high body temperature. Malignant or fatal catatonia is a state of catatonia with hyperthermia.

The similarity between the presentations of the above syndromes and NMS, confirms that the diagnostic criteria of NMS are not specific and require a revision. It appears we do not have the proper knowledge regarding the patho-physiolgy and neurological mechanisms of NMS. Therefore, the disorder and all other similar syndromes may belong to a broader category of CNS problems (29).

To sum up, we strongly recommend the need for further studies regarding proper definition of NMS criteria, in order to prevent the under diagnosis of the disorder, especially following the higher rate of prescribing atypical anti-psychotics.

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